Review Article

Review of basal-plus insulin regimen options for simpler insulin intensification in people with Type 2 diabetes mellitus

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Abstract

Aims To identify simple insulin regimens for people with Type 2 diabetes mellitus that can be accepted and implemented earlier in primary and specialist care, taking into consideration each individual's needs and capabilities.

Methods Using randomized clinical trials identified by a search of the PubMed database, as well as systematic reviews, meta-analyses and proof-of-concept studies, this review addresses topics of interest related to the progressive intensification of a basal insulin regimen to a basal-plus regimen (one basal insulin injection plus stepwise addition of one to three preprandial short-acting insulin injections/day) vs a basal-bolus regimen (basal insulin plus three short-acting insulin injections per day) in people with Type 2 diabetes. The review explores approaches that can be used to define the meal for first prandial injection with basal-plus regimens, differences among insulin titration algorithms, and the importance of self-motivation and autonomy in achieving optimum glycaemic control.

Results A basal-plus regimen can provide glycaemic control equivalent to that obtained with a full basal-bolus regimen, with fewer injections of prandial insulin. The first critical step is to optimize basal insulin dosing to reach a fasting glucose concentration of ~6.7 mmol/l; this allows ~40% of patients with baseline HbA_{1c} >75 mmol/mol (9%) to be controlled with only one basal insulin injection per day.

Conclusions Compared with a basal-bolus regimen, a basal-plus insulin regimen is as effective but more practical, and has the best chance of acceptance and success in the real world.

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Introduction

Type 2 diabetes mellitus is a progressive disease, and most people with this condition eventually need insulin therapy to maintain the tight glycaemic control that is essential to reduce the risk of microvascular and macrovascular complications [1]. Although the benefits of early insulin treatment are well established, there are often considerable delays in initiating insulin in people with Type 2 diabetes who have sub-optimum glycaemic control on oral therapy. In a study conducted in the UK, the median time to initiation of insulin treatment after oral treatment was >7 years and this occurred at a mean HbA_{1c} level of 79–84 mmol/mol (9.4–9.8%) [2]. Similar data were obtained in the USA [insulin initiated at a mean HbA_{1c} of 81 mmol/mol (9.6%), 3 years after the start of combination oral antidiabetic drug (OAD) therapy] [3] and France [mean HbA_{1c} 77 mmol/mol (9.2%) at insulin initiation] [4], whereas in Germany basal insulin was initiated at a lower mean HbA_{1c} of 64 mmol/mol (8.0%) [5].

Intensification after the initiation of basal insulin also occurs late, as shown in a UK study in which intensification occurred after a median period of 3.7 years in people with Type 2 diabetes whose HbA_{1c} was ≥58 mmol/mol (7.5%) [6]. Only 30% of the people with Type 2 diabetes eligible for treatment intensification actually received it and, of those who received intensification, 47% received bolus insulin, 43% received premixed insulin and 10% received a glucagon-like peptide-1 (GLP-1) receptor agonist. Intensification in these three groups occurred at mean HbA_{1c} values of 78, 81 and 78 mmol/mol (9.3, 9.6 and 9.3%), respectively [6]. Similar delays in insulin intensification were reported in the USA and Canada, especially in primary care [7].

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> **What's new?**
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> • Insulin initiation and intensification in people with Type 2 diabetes mellitus are often delayed, increasing the risk of complications.
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> • Simplified regimens may lead to greater acceptance and earlier implementation of insulin therapy.
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> • This evidence-based review shows that a basal-plus insulin regimen can provide glycaemic control equivalent to that obtained with a full basal-bolus regimen, with fewer injections of prandial insulin.
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> • A basal-plus insulin regimen may therefore have a better chance of acceptance and success in the real world than a full basal-bolus regimen through improved glycaemic control and consequent reduction in the risk of complications of diabetes.

Data from the Europe-wide PANORAMA study identified numerous factors associated with poor glycaemic control. These include poor adherence of individuals to medication and lifestyle recommendations, greater treatment regimen complexity and physician-reported unwillingness of the person with diabetes to intensify treatment [8]. Physicians themselves may also be reluctant to initiate and intensify insulin therapy. Reasons include inexperience with the use of insulin and intensification algorithms [9], poor motivation [10,11], insufficient time to educate people with Type 2 diabetes, together with lack of clear guidelines [10,11], and potential adverse effects such as weight gain and hypoglycaemia [12]. In elderly people with Type 2 diabetes in the USA, early insulin initiation allowed better glycaemic control without an increase in hypoglycaemia; nevertheless, many physicians fear hypoglycaemia and this can lead to delays in insulin initiation in elderly people [13].

Reluctance of people with Type 2 diabetes to start insulin therapy may be based on an inability to cope with complex regimens and on a number of fears: that their diabetes is deteriorating; that their activities of daily living will be restricted; that insulin therapy may increase the risks of hypoglycaemia and weight gain; and that injections will be unpleasant [9,14]. Engaging with individuals to discuss the benefits of treatment compared with potential drawbacks may improve their willingness to progress to insulin and adhere to therapy. To this end, primary care physicians should be involved in all stages of insulin therapy [15]. These patient-based difficulties in initiating insulin therapy point to the need for a patient-centred approach and shared decision-making [16].

For insulin initiation, the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) [16], and the American Association of Clinical Endocrinologists (AACE) and the American College of Endocrinology (ACE) [17] recommend basal insulin, whereas basal or premixed insulin [International Diabetes Federation (IDF), 2014 [18]] and basal, basal-bolus or premixed insulin [National Institute for Health and Care Excellence (NICE), 2015 [19]] are recommended by other organizations.

After optimum basal insulin titration, options for intensification include addition of mealtime insulin (one to three injections of rapid-acting insulin), transitioning to twice- and then thrice-daily premixed insulin or addition of a glucagon-like peptide-1 (GLP-1) receptor agonist [1,16]. The addition of a GLP-1 receptor agonist to basal insulin in people with Type 2 diabetes whose HbA_{1c} remains above goal, despite optimum dose titration, is a recent and attractive option for treatment intensification [16,17], but is outside the scope of the present review.

Full basal-bolus therapy comprises basal insulin plus three short-acting insulin injections per day. The term 'basal-plus therapy' is usually used to describe a regimen comprising one basal insulin injection and the stepwise addition of one to three preprandial short-acting insulin injections per day [20–23]. These definitions of 'basal-bolus' and 'basal-plus' are used in the present review. Some authors use the term 'basal-plus therapy' to refer to basal insulin plus one short-acting insulin injection per day and 'basal-bolus therapy' to refer to basal insulin plus two to three prandial injections per day [15,16,24]. Premixed insulin can be initiated with one and intensified to three injections per day [25–27].

Recommendations for insulin intensification in people with Type 2 diabetes differ among guidelines, and include a basal-plus or basal-bolus regimen (AACE and ACE, 2016 [17]), basal-plus, basal-bolus or premixed insulin regimens (ADA and EASD, 2015 [16], ADA, 2017 [1]; multiple daily injections (IDF, 2014 [18]), and intensification from basal to premixed or basal-bolus insulin regimens, or from premixed insulin to premixed plus bolus insulin or basal-bolus insulin regimens (NICE, 2015 [19]).

In daily practice, the choice of initial insulin regimen varies among countries, with basal-bolus and premixed insulin regimens demonstrating equivalent glycaemic control and body-weight gain [28,29]. Two recent meta-analyses also suggest that basal-plus or basal-bolus insulin regimens are as effective as premixed insulin regimens in people with Type 2 diabetes, with no significant differences in hypoglycaemia and weight gain [30,31]. It should be noted that the higher costs associated with the intensive blood glucose monitoring needed with a full basal-bolus regimen [32] may make this option impractical in many countries.

Choosing an appropriate insulin regimen should thus be based on an individual's characteristics and be patient-centric [15,27,33,34]. Sufficient frequency of blood glucose monitoring to allow appropriate adaptation of insulin doses is also critical for the success of the insulin regimen [28]. This should be taken into account when considering adherence

and, in some countries, when considering the costs associated with treatment.

The progressive nature of Type 2 diabetes suggests that stepwise intensification of insulin therapy would be a more logical and simpler approach to treatment, and also the most acceptable to both patients and physicians [35,36].

Our comprehensive evidence-based review focuses on the benefits of progressive intensification of a basal insulin regimen to basal-plus and basal-bolus regimens in people with Type 2 diabetes. We discuss different approaches for defining the meal for the first prandial injection in basal-plus studies, differences among insulin titration algorithms, and the importance of individual motivation and autonomy in achieving optimum glycaemic control.

Scope and methods

The present review focuses predominantly on randomized clinical trials of insulin intensification regimens. To this end, a literature search of the PubMed database was carried out on 17 February 2016 using the following limits: article types: clinical study, clinical trial; published between 1 January 2011 and the search date. The search ['insulin AND type 2 AND (stepwise OR patient-managed OR intensification OR glargine plus OR premixed)'] addressed topics of interest with respect to basal-plus and basal-bolus regimens. Using the results of the search and additional studies identified by the authors, we have focused primarily on studies that involved the use of full stepwise basal-plus insulin regimens, but systematic reviews, meta-analyses and proof-of-concept studies were also identified and are discussed.

Rationale and proof-of-concept studies

As first shown by Monnier *et al.* in 2003 [37], the relative contribution of postprandial hyperglycaemia to overall hyperglycaemia is higher at low HbA_{1c} levels. It is therefore logical to first decrease fasting hyperglycaemia with adequate titration of basal insulin. Addition of prandial insulin to control postprandial hyperglycaemia can then further improve HbA_{1c}.

Five proof-of-concept studies have shown that adding one injection of prandial insulin to a basal insulin regimen can improve glycaemic control. In the OPAL study [38], patients receiving insulin glargine and OADs were randomized to receive a single injection of insulin glulisine before breakfast or the largest meal of the day. The two regimens were similarly effective in reducing HbA_{1c} from baseline levels of 56–57 mmol/mol (7.3–7.4%) to 52–53 mmol/mol (6.9–7.0%) [38]. Owens *et al.* [39] also determined that adding a single injection of insulin glulisine to insulin glargine, before the main meal, improved HbA_{1c} by 3–4 mmol/mol (0.3–0.4%), without an increase in hypoglycaemia. In the ELEONOR study [40], addition and titration of insulin glargine followed by a single dose of rapid-acting insulin at

the meal with the highest postprandial excursion was associated with improvements in HbA_{1c} and a low incidence of hypoglycaemia, and with marked improvements in treatment satisfaction. These improvements occurred whether patients used standard self-monitoring of blood glucose or 'telecare'. In the START study, also, a single bolus of insulin glulisine added at breakfast in patients receiving insulin glargine was as effective in improving HbA_{1c} when implemented using either patient-managed or physician-managed titration algorithms [41]. Davidson *et al.* [21] showed that, in terms of HbA_{1c} reduction, insulin glulisine once or twice daily was non-inferior to insulin glulisine three times daily, but that more patients reached their HbA_{1c} target with three injections.

In addition to these proof-of-concept studies, we have reviewed other studies in which a stepwise basal-bolus regimen incorporating one to three injections of prandial insulin has been used successfully in people with Type 2 diabetes whose glycaemia was insufficiently controlled with one daily injection of basal insulin.

Results

The designs and results of the full stepwise basal-plus studies retrieved by the literature search are summarized in Tables 1 and 2. These studies raise a number of questions: (1) Is addition of prandial insulin necessary in all people with Type 2 diabetes if basal insulin is properly titrated? (2) For people with Type 2 diabetes on basal insulin who require intensification, is a stepwise approach to addition of prandial insulin an effective alternative to a full basal-bolus approach? (3) For people with Type 2 diabetes who do require prandial insulin and for whom a stepwise basal-plus approach is chosen, which meal should be targeted for the first injection? (4) Should titration of prandial insulin be based on pre- or postprandial glycaemia or on prandial excursion? (5) Is it always necessary for the physician to titrate the insulin, or can patient-directed titration be equally effective?

An additional question which frequently arises when initiating prandial insulin using a basal-plus approach is how existing treatment with an insulin secretagogue (e.g. a sulfonylurea) should be managed. Current ADA and EASD guidelines indicate that sulfonylureas, dipeptidyl peptidase-4 inhibitors and GLP-1 receptor agonists are typically stopped when prandial or premixed insulin therapy is initiated [16].

Is addition of prandial insulin necessary in all people with Type 2 diabetes if basal insulin is properly titrated?

Basal insulin is designed to suppress hepatic glucose production and improve fasting hyperglycaemia. The basal insulin dose needs to be optimized before adding prandial insulin [42]. As shown in Table 1, in four studies, basal insulin was titrated in the run-in period prior to randomization. In three of these studies [22,23,42], the target fasting plasma glucose

Table 1 Design of clinical trials including a stepwise basal-plus insulin regimen

Author (study)	Patients at entry	Basal insulin Type of insulin and time of administration	Duration of run-in and glycaemic target	Randomization	Meal for first injection of prandial insulin

Meneghini et al. [20] (STEP)	N = 345 On basal insulin + OADs	Detemir at bedtime	Run-in 12 weeks before randomization; target FPG, 4.0–6.0 mmol/l	• Patients with HbA1c ≥53 mmol/mol (7.0%)
				• Randomized (three periods of 12 weeks) to addition of:
				  ○ Insulin aspart 1–3 times daily (SimpleSTEP; n = 150)
				  ○ Insulin aspart 1–3 times daily (ExtraSTEP; n = 146)
				• Glycaemic target:
				  ○ SimpleSTEP: Pre-meal PG, 4.0–6.0 mmol/l; bedtime PG, 4.0–8.0 mmol/l
				  ○ ExtraSTEP: 2-h post-meal PG, 4.0–8.0 mmol/l
					SimpleSTEP: Largest meal as determined by the patient ExtraSTEP: Meal with largest post-meal glucose increase

Bowering et al. [25] (PARADIGM)	N = 426 On OADs without insulin	Glargine at bedtime	No run-in; Target FPG, 4.5–6.0 mmol/l	• Randomized to:
				  ○ Insulin lispro mix25 (N = 214)
				  ○ Insulin glargine at bedtime then insulin lispro 1–3 times daily (N = 212)
				• Lead in 8–12 weeks for insulin glargine, 4–12 weeks for insulin lispro mix25 at bedtime
				• Additional insulin injections could be initiated by the investigator weekly up to week 8, or biweekly from week 8 to 48
				• Target (pre-meal): 4.5–6.0 mmol/l
					Meal prior to meal with highest premeal glucose value

Raccah et al. [22] (OSIRIS)	N = 811 On basal insulin + OADs	Glargine at dinner or bedtime	Run-in 6 months before randomization; target FBG, 4.4–6.1 mmol/l	• Only patients with HbA1c >53 mmol/mol (7%) and FBG ≤6.7 mmol/l randomized for 12 months (N = 476) (N = 272 FBG not at target)
				• Randomized to addition of:
				  ○ Group 1: Metformin + insulin glulisine 3 times daily (n = 153)
				  ○ Group 2: Metformin + stepwise addition of insulin glulisine 1–3 times daily (n = 199)
					Groups 2 and 3: Meal with highest postprandial BG

Table 1 (*Continued*)

Author (study)	Patients at entry	Basal insulin Type of insulin and time of administration	Duration of run-in and glycaemic target	Randomization	Meal for first injection of prandial insulin
				o Group 3: Metformin + insulin secretagogue + stepwise addition of insulin glulisine 1–3 times daily ($n = 124$) • Glycaemic target for glulisine • Postprandial BG 6.1–8.9 mmol/l	
Edelman *et al.* [42] (AUTONOMY)	NA On basal insulin + OADs	Glargine at bedtime	Run-in 6 weeks before randomization; Target FPG, 5.6 mmol/l	• 2 independent, similar studies ($N = 528$, $N = 578$) • Sulfonylurea or glinide discontinued • If HbA$_{1c}$ >53 mmol/mol (7.0%), randomized for 24 weeks to self-titration algorithms based on pre-meal PG target of 4.7–6.3 mmol/l, with (to adjust dose of insulin lispro) either: o 1 reading/day • Median of readings of 3 previous days	First injection of insulin Lispro prior to breakfast, then lunch, then dinner

Rodbard *et al.* [23] (FullSTEP)	$N = 1008$
	On basal insulin + OADs
		Detemir at bedtime	Run-in 8 weeks before randomization; Target FPG, 4.0–7.2 mmol/l	• Only patients with HbA$_{1c}$ >53 mmol/mol (7%) randomized for 32 weeks
				• Randomized to:
				  o Stepwise addition of 1–3 insulin aspart ($n = 201$) at randomization and weeks 11 and 22
				  o Full basal-bolus therapy (insulin aspart; $n = 200$)
				• Self-titration with pre-meal PG target of 4.0–7.2 mmol/l
					Stepwise group: Largest meal (meal with highest carbohydrate intake, as determined by the patient)

Riddle *et al.* [24]	$N = 691$
	On OADs without insulin
		Glargine	No run in
			Target FBG, 5.6 mmol/l
				• Only patients with HbA$_{1c}$ >53 mmol/mol (7.0%) randomized for 60 weeks; sulphonylurea stopped
				• Randomized to:
				  o Premixed insulin 30/70 twice daily ($N = 194$)
				  o Insulin glargine once daily + insulin glulisine once daily ($N = 194$)
					Meal with highest postprandial glucose value

Table 1 (Continued)

Author (study)	Patients at entry	Basal insulin		Duration of run-in and glycaemic target	Randomization	Meal for first injection of prandial insulin
		Type of insulin and time of administration				
Giugliano et al. [26]	N = 344 On OADs, without insulin, light breakfast	Glargine in the morning or at bedtime		No run-in; Target FBG, 4.7–6.3 mmol/l	○ Insulin glargine once daily + stepwise addition of 1–3 insulin glulisine (N = 194) • Glycaemic target: pre-meal PG 3.9–5.5 mmol/l • Randomized for 48 weeks (pioglitazone stopped and sulphonylurea stopped at second insulin injection) to: ○ Insulin lispro mix25/50, 1–3 injections (N = 171) ○ Insulin glargine + 1–3 injections of insulin lispro (N = 173) • Glycaemic target: pre-meal BG 4.7–6.3 mmol/l	Meal with highest 2 h postprandial BG (lunch or dinner)
Jain et al. [43]	N = 484 On OADs without insulin	Glargine in the morning		No run-in; Target FBG, 4.5–5.5 mmol/l	• Patients randomized for 36 weeks to: ○ Insulin glargine + 1–3 injections of insulin lispro (N = 242) ○ Insulin lispro mix50, 1 to 3 injections (N = 242) • Glycaemic target: fasting and pre-meal BG <5.5 mmol/l	Meal with next largest pre-meal or bedtime glucose value
Malek et al. [44]	N = 403 On OADs without insulin	Detemir at bedtime		No run-in	• Patients randomized for 50 weeks to: ○ Insulin detemir + 1–3 injections of insulin aspart (N = 200) ○ Biphasic insulin aspart 30 1–3 injections (N = 203) • Dose of insulin aspart adjusted based on next pre-meal BG	Largest meal

BG, blood glucose; FBG, fasting blood glucose; FPG, fasting plasma glucose; NA, data not available; OAD, oral antidiabetic drug; PG, plasma glucose.

Table 2 Results of basal-plus regimens in studies including this regimen and of basal-bolus regimen when available

Author	HbA1c, mmol/mol (%) Baseline[1]	Endpoint[1]	% at target <53 mmol/mol (7.0%)[3] or ≤53 mmol/mol (7.0%)[4]	FPG/FBG[1] Baseline	Endpoint	Change from baseline in body weight (kg)[1] Endpoint	Insulin dose at endpoint: Total (basal; prandial)[1]	Number of insulin injections/day at endpoint (% of patients) 1 (basal)	2	3	4	Number of injections/day at endpoint (% of patients who received prandial insulin)[2] 2	3	4
Meneghini et al. [20] (STEP)														
Basal-plus:														
SimpleSTEP	72 (8.7)	58 (7.5)	31[3]	8.1 mmol/l	7.5 mmol/l	+2.7	1.25 U/kg/day (0.72; 0.53)	NA	NA	NA	77.2	NA	NA	NA
ExtraSTEP	74 (8.9)	61 (7.7)	27[3]	8.3 mmol/l	7.4 mmol/l	+2.0	1.37 U/kg/day (0.84; 0.53)	NA	NA	NA	76.7	NA	NA	NA
Bowering et al. [25] (PARADIGM)														
Basal-plus	75 (9.0)	56 (7.3)	39.1[3]	10 mmol/l	6.3 mmol/l	+2.9	0.71 U/kg/day	42.9	10.9	26.6	19.6	19.0	46.7	34.3
Raccah et al. [22] (OSIRIS)														
Basal-bolus (group 1)	69 (8.5)	61 (7.7)	27.1[4]	5.8 mmol/l	~6.1 mmol/l	+2.0	66 U/day (37; 29)	–	1.4	1.4	92	NA	NA	NA
Basal-plus (group 2)	68 (8.4)	63 (7.9)	18.4[4]	5.8 mmol/l	~6.1 mmol/l	+1.3	60 U/day (40; 20)	–	30.5	40.1	22.8	30.5	40.1	22.8
Basal-plus+ secretagogue (group 3)	67 (8.3)	63 (7.9)	22.4[4]	5.9 mmol/l	~6.1 mmol/l	+1.9	57 U/day (40; 17)	–	35.0	35.8	19.5	35.0	35.8	19.5
Edelman et al. [42] (AUTONOMY)														
Study A														
Q1D	67 (8.3)	56 (7.3)	49.8[4]	~6.6 mmol/l	6.6 mmol/l	+2.2[5]	114.1 U/day (66.4; 47.7)	–	31.5	25.8	42.7	31.5	25.8	42.7
Q3D	68 (8.4)	57 (7.4)	42.5[4]	~6.6 mmol/l	6.3 mmol/l	+3.0[5]	118.1 U/day (63.5; 54.6)	–	31.0	25.3	43.7	31.0	25.3	43.7
Study B														
Q1D	67 (8.3)	56 (7.3)	49.3[4]	~6.6 mmol/l	6.3 mmol/l	+2.5[5]	104.4 U/day (59.9; 44.5)	–	35.4	29.5	35.1	35.4	29.5	35.1
Q3D	68 (8.4)	57 (7.4)	42.4[4]	~6.6mmol/l	6.3 mmol/l	+2.0[5]	114 U/day (65.2; 48.8)	–	34.5	30.7	34.8	34.5	30.7	34.8
Rodbard et al. [23] (FullSTEP)														
Basal-bolus	63 (7.9)	51 (6.8)	63.3[3]	6.9 mmol/l	7.0 mmol/l	+3.7	1.2 U/kg/day (0.6; 0.6)	–	–	–	100	–	–	100
Basal-plus	63 (7.9)	52 (6.9)	55.9[3]	7.0 mmol/l	7.1 mmol/l	+0.4	1.1 U/kg/day (0.6; 0.5)	–	17	27	40	17	27	40
Riddle et al. [24]														
Basal-plus	79 (9.4)	55 (7.2)	45[3]	11.5 mmol/l	6.8 mmol/l	+6.8	1.1 U/kg/day	38	23	21	18	37.8	33.6	28.6
Giugliano et al. [26]														
Basal-plus	76 (9.1)	60 (7.6)[5]	36.2[3]	9.6 mmol/l	6.3 mmol/l	+2.3	0.57 U/kg/day (0.39; 0.18)	45	21	23	11	38.0	42.3	19.7
Jain et al. [43]														
Basal-plus	78 (9.3)	58 (7.5)[5]	43[4]	9.6 mmol/l[5]	6.5 mmol/l[5]	+3.2[5]	0.51 U/kg/day[5]	45.8	27.1	20.0	7.1[6]	50.0	36.9	13.1[6]
Malek et al. [44]														
Basal-plus	70 (8.6)	57 (7.4)	40.3[3]	NA	6.0 mmol/l	+3.2	87.9 U/day	NA	NA	72.4 on ≥3 injections	NA	NA	NA	NA

FBG, fasting blood glucose; FPG, fasting plasma glucose; NA, data not available; Q1D, prandial insulin titration based on one plasma glucose reading/day; Q3D, prandial insulin titration based on median of readings of 3 previous days.

[1]Values represent mean unless specified otherwise. [2]Data corrected for the percentage of patients who received only one injection of basal insulin. [3]HbA1c target at endpoint <53 mmol/mol (7.0%). [4]HbA1c target at endpoint ≤53 mmol/mol (7.0%). [5]Least squares mean value. [6]Includes one patient who received five injections/day (2 × insulin glargine, 3 × insulin lispro).

(FPG) or fasting blood glucose (FBG) level during the run-in period was ≤5.6–7.2 mmol/l and the mean FPG or FBG at randomization was ≤7.0 mmol/l. In these studies, a relatively low percentage (20–44%) of the participants assigned to stepwise addition of rapid-acting insulin required three bolus prandial injections (Table 2) [22,23,42]. In contrast, in the STEP study [20], insulin detemir was not sufficiently titrated (mean FPG at baseline, ~8.3 mmol/l) and >70% of participants required three prandial injections.

In studies in which insulin glargine was titrated in a lead-in period after randomization, ~40% (range: 38–46%) of participants were controlled with only one injection of basal insulin and mean FPG levels were estimated at between 6.3 and 6.5 mmol/l at endpoint [24–26,43]; thus, if basal insulin is properly titrated, only ~60% of patients will require the addition of prandial insulin.

For people with Type 2 diabetes on basal insulin who require intensification, is a stepwise approach to addition of prandial insulin an effective alternative to a full basal-bolus approach?

In the OSIRIS study [22], in which stepwise addition of prandial insulin and a full basal-bolus regimen were compared, non-inferiority of glycaemic control was not achieved and post-breakfast and post-dinner blood glucose reductions were significantly smaller for the stepwise approach than for the basal-bolus regimen. However, the efficacy of the stepwise approach was considered close to that of the basal-bolus approach, with significantly less weight gain and no significant differences in hypoglycaemia or in the proportion of participants achieving target HbA$_{1c}$ ≤53 mmol/mol (7.0%) at the 12-month endpoint [22]. In the study by Rodbard et al. [23], stepwise addition of prandial insulin for 32 weeks was non-inferior to a basal-bolus regimen for glycaemic control (HbA$_{1c}$), with similar weight gain, fewer hypoglycaemic episodes and higher participant satisfaction.

As shown in Table 2, in OSIRIS and in the study by Rodbard et al. [23], the majority of participants assigned to stepwise addition of prandial insulin did not require three doses of prandial insulin. The same conclusion can be reached for all other studies listed in Table 2: of all participants who received prandial insulin 19–50% received one prandial injection per day, 34–47% received two prandial injections per day and 13–44% received three prandial injections per day. In these calculations, the data were corrected for the percentage of participants who received only one injection of basal insulin. These results suggest that a full basal-bolus regimen is probably not necessary for the majority of patients at the time of insulin intensification after appropriate basal insulin titration.

Interestingly, and although the results are outside the scope of the present review, four studies have compared a basal-plus regimen (one to four injections) with a stepwise premixed insulin regimen (one to three injections; Table 1;

[25,26,43,44]) and, with minor exceptions, there were no differences between regimens in overall hypoglycaemia rate, weight change, or insulin dose; however, results varied with regard to the mean number of injections (no difference [25,26]; a higher number in the premixed-treated group [43] or a higher number in the basal-plus group [44]) and the percentage of participants reaching target HbA$_{1c}$ (no difference [25,43,44] or a higher percentage in the premixed-treated group [26]).

For people with Type 2 diabetes who do require prandial insulin and for whom a stepwise basal-plus approach is chosen, which meal should be targeted for the first injection?

Largest meal with highest carbohydrate intake as determined by the individual
In the FullSTEP study [23], the SimpleStep arm of the STEP study [20] and the study by Malek et al. [44], insulin intensification involved the stepwise addition of insulin aspart starting before the largest meal.

Most hyperglycaemic meal as determined by highest postprandial or next pre-meal glycaemic value
In the OSIRIS study [22], and in the studies by Riddle et al. [24] and Giugliano et al. [26], the first daily bolus injection was administered before the meal with the highest postprandial glucose level. In the ExtraStep arm of the STEP study [20], the first daily bolus injection was administered before the meal with the highest postprandial glucose increase. In the STEP study (in which titration of detemir was not optimal), there was no difference in efficacy between participants whose first prandial injection was administered at the meal determined to be the largest, or at the meal with the highest postprandial excursion. In the PARADIGM study [25] and the study by Jain et al. [43], insulin lispro was first administered at the main meal, defined as the meal followed by the highest next pre-meal glycaemia.

Breakfast
In most studies using a stepwise approach, prandial insulin was initiated with the main meal of the day, as defined using glucose levels or the perception of the individual [20,22,23,25,40,46]; however, Monnier et al. [47,48] found that the highest plasma glucose excursion typically occurs in the morning. Moreover, in their analysis of self-monitored blood glucose data from across Europe and North America, Schaefer et al. [49] showed that, before starting basal insulin, the highest postprandial glucose level and increment of the day generally occurred after breakfast. By contrast, after 24 weeks of insulin glargine administration, the greatest postprandial increment occurred after breakfast (46% of participants), while the highest postprandial glucose level most often occurred after dinner (44% of participants).

A number of studies have evaluated breakfast as an option for the first prandial insulin injection, confirming the

observations of Shaefer *et al.* [49] and Monnier *et al.* [47,48]. In the OPAL study [38], addition of a single bolus of insulin glulisine at breakfast to insulin glargine and OADs was equally effective in improving HbA$_{1c}$ as glulisine at the main mealtime. In the START study [41], all participants who required insulin intensification had once-daily bolus insulin glulisine at breakfast. This regimen was chosen to capitalize on the fact that most people with Type 2 diabetes receiving basal insulin routinely test their blood glucose in the morning, and that addition of a breakfast prandial insulin self-titration algorithm requires only one extra self-monitoring test later the same morning, thereby maximizing convenience [41]. Approximately 25% of participants achieved HbA$_{1c}$ ≤53 mmol/mol (7.0%) in this study.

In the STEP study [20], when the main meal was defined as the one with the largest post-meal glucose increase (Extra-Step), a higher percentage of participants received a bolus injection at breakfast, whereas when the main meal was defined as the largest self-reported meal, a higher percentage of participants received injections at lunch and dinner. Even in patients who ate light breakfasts, the mean blood glucose values after breakfast were not very different from those after lunch and dinner, suggesting that administering the first injection at breakfast might result in a similar improvement in glycaemic control as administration at lunch or dinner [26]. In the AUTONOMY study, which was designed to explore insulin intensification with dose titration daily vs every 3 days in individuals receiving basal insulin, sequential addition of prandial insulin, beginning with a dose with the first meal of the day, resulted in significant improvements in glycaemic control, with ~50% of participants achieving HbA$_{1c}$ ≤53 mmol/mol (7.0%) [42].

These findings suggest that, for patients who eat breakfast, this may be a suitable and convenient meal at which to administer the first prandial insulin injection after optimization of insulin glargine. For patients who do not eat breakfast, the first injection could be taken at lunch [42] or with their evening meal if the largest of the day, based on social and cultural habits.

Should titration of prandial insulin be based on pre- or post-meal glycaemia or on prandial excursion?

In most studies, whatever the criteria used to define the first meal for injection of bolus prandial insulin, titration was based on next pre-meal and bedtime glycaemic values [20,23–26,42,43], with upper limits to the pre-meal glycaemic target ranges of 5.5–7.2 mmol/l (Table 1); however, in the STEP [20] and OSIRIS [22] studies, titration was based on postprandial glycaemia, with upper limits to the target ranges of 8.0 and 8.9 mmol/l, respectively (Table 1). In the STEP study [20], titration based on pre-meal glucose values (SimpleSTEP) was as effective as titration based on post-meal values despite fewer self-monitored blood glucose measurements. Pre-meal values thus appear easier in daily life for

patients to measure and offer less variability in measurement than post-meal tests. If the time between meals is very long, however, and especially for people with Type 2 diabetes in Spain and other countries who eat a late evening meal, 2-h post-meal glycaemic values may be more appropriate.

Is it always necessary for the physician to titrate the insulin, or can self-directed titration be as effective?

There is evidence from basal-plus studies to suggest that people with Type 2 diabetes can safely and effectively self-titrate both basal and prandial insulin. In the ELEONOR study [40,46], conventional self-monitored blood glucose proved as effective as a telecare system for titrating one prandial insulin glulisine injection in participants already on basal insulin, and was associated with high levels of satisfaction [40]. Titration was based on reaching a 2-h postprandial glucose level <7.8 mmol/l. In the START study [41], a patient-managed titration algorithm for a single bolus injection of insulin glulisine was as effective as a physician-managed algorithm. The titration algorithm mandated a 1-unit dose increase per day to reach a 2-h postprandial glycaemia of 5.0–8.0 mmol/l; however, the most robust data in support of a patient-centred approach to insulin titration come from the AUTONOMY studies, which enrolled people with Type 2 diabetes who were inadequately controlled on basal insulin [42]. These two studies, conducted in primary and secondary care, involved comparison of two patient self-titration algorithms after optimization of basal insulin, with adjustment of the dose of prandial insulin lispro every day (1- to 2-unit change based on pre-meal blood glucose) or every 3 days (2- to 4-unit change based on median of pre-meal blood glucose values over the previous 3 days) to reach a pre-meal glucose target of 4.7–6.3 mmol/l. Investigators added prandial insulin injections as required. Both patient-driven algorithms showed significant and equivalent reductions in HbA$_{1c}$ and a low incidence of hypoglycaemia, both in the overall study population and in a subgroup of elderly individuals. Approximately 61% of participants required ≤2 doses of prandial insulin rather than a full basal-bolus regimen [42]; such a regimen simplifies treatment and could enhance compliance with insulin therapy.

Interestingly, in an observational study performed under real-life conditions, the mean number of times that glucose was measured across insulin regimens was only once per day [28].

As the above studies illustrate, the key to good glycaemic control lies in the provision of simple titration algorithms that allow and motivate patients to manage their insulin therapy. Knowledge of diabetes and its treatment empowers individuals to gain control of their disease, and this in turn reduces the burden on physicians [50].

Daily insulin dose titration of 1 unit per day, to reach target glycaemia levels < 4.7–6.3 mmol/l or 4.0–7.2 mmol/l before the next meal, as in the AUTONOMY and FullSTEP studies, respectively, appears the most feasible and practical

algorithm, allowing patients to achieve mean endpoint HbA_{1c} values of 51–57 mmol/mol (6.8–7.4%) [23,42]. If meals are widely spaced, a daily titration based on a 2-h post-meal glucose target of 5.0–8.0 mmol/l, as in the START study, appears to be a good, practical alternative [41].

Conclusions

Observational studies have shown that insulin initiation and intensification are taking place too late. As a result, people with Type 2 diabetes remain at high HbA_{1c} levels for a long time and this leaves them at high risk of developing complications. There is thus a need for simpler insulin regimens that can be taught and implemented easily and earlier in a primary or specialist care setting; in all cases, the individual's needs and capabilities should be taken into consideration.

The present review has shown that a basal-plus regimen can provide equivalent glycaemic control to a full basal-bolus regimen, with fewer injections of prandial insulin. The first critical step is to optimize basal insulin dosing to reach a fasting glucose of ~6.7 mmol/l; this allows ~40% of patients with baseline HbA_{1c} >75 mmol/mol (9%) to be controlled with only one basal insulin injection per day.

For individuals whose regimen will be intensified using a basal-plus regimen, the meal for the first injection must be chosen. This review has shown that there is little difference in efficacy among insulin intensification regimens that use different definitions for the main meal of the day. Breakfast appears to be the best choice both from a glycaemic point of view (as it is the meal with the highest glycaemic excursion) and from a practical point of view, as the person can usually inject at home; however, some flexibility is needed for people taking no or very light breakfasts, with the first injection then taken at lunch or at supper, whichever is the largest meal of the day, based on cultural or social habits.

The glycaemic target (preprandial or postprandial) for titration of prandial insulin dose must also be chosen. Postprandial glycaemia measurement appears to be more complicated for people with Type 2 diabetes and potentially more variable in real life than preprandial glycaemia. Since preprandial and postprandial glycaemia give equivalent results, preprandial glucose levels appear more practical in daily practice; however, in countries where there is usually a long interval between meals, as with a late supper, titration based on 2-h postprandial glycaemia may be more appropriate.

The algorithm used for dose titration should be as simple as possible for the patient; in this respect, dose adaptation based on the daily measurement of glycaemia, as in the AUTONOMY, FullSTEP and START studies, appears the simplest.

Finally, studies have shown the importance of empowerment and autonomy of the individual in managing dose titration. A number of studies have shown equivalent glycaemic control with patient- vs physician-directed titration, with higher satisfaction associated with patient-directed algorithms.

In conclusion, therefore, compared with a basal-bolus insulin regimen, a basal-plus insulin regimen appears to be as effective but more practical. It is ideal, where circumstances permit, to initiate this regimen in association with a simple, patient-directed algorithm which incorporates preprandial glucose targets, using breakfast as the meal for the first prandial injection. This approach should allow insulin intensification to have the best chance of acceptance and success in the real world.

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